Correlating exposure to environmental tobacco smoke exposure with increased incidence of lung cancer in non smokers : is cotinine a valid marker ?

M.B. Roberfroid

Department of Pharmaceutical Sciences, Universite Catholique de Louvain, UCL 7369 B-1200, Brussels Belgium; fax: 32 2 764 7254

ABSTRACT

Environmental Tobacco Smoke (ETS) is a complex mixture of Exhaled Mainstream (EMS) and Sidestream Smoke (SS) composed of gases and Respirable Suspended Particles (RSP). It is both a highly diluted and an aged mixture the composition of which is difficult to assess. Based mainly on syllogisms it has been hypothesized that exposure to low levels of ETS increases the risk of lung cancer in nonsmokers. There is no question that nonsmokers living in the presence of smokers are exposed to tobacco smoke constituents. But, to conclude on the significance of such an exposure, in term of increased incidence of lung cancer in non smokers, can only rely on a quantitative biomonitoring of exposure to agents proven to play a causative role in lung carcinogenesis. Nether nicotine nor its metabolites are likely to be precise markers of exposure to such chemicals. Molecular epidemiology offers a promising, but still to be validated, tool to meet such a challenge by measuring proteins and/or DNA adducts in serum or urine samples.

Key words: tobacco smoke, cotinine, lung cancer, cancer risks.

INTRODUCTION

ENVIRONMENTAL TOBACCO SMOKE (ETS) is a complex mixture of exhaled mainstream smoke (EMS) and sidestream smoke (SS) composed of gases and respirable suspended particles (RSP) [see Table 1 (1-3) for definitions]. It has been hypothesized (4,5) that exposure to low levels of ETS increases the risk of lung cancer in non smokers. Two syllogisms support this hypothesis: [1] a) if ETS is chemically analogous to mainstream cigarette smoke (MS) ; and b). MS is known to cause lung cancer in active smokers; then c). ETS causes lung cancer in passive smokers; [2)] a): if ETS contains lung carcinogens, and b). it is generally assumed that no dose threshold exists for carcinogens: then c). ETS is a lung carcinogen. There is no question that non smokers living in the presence of smokers are exposed to tobacco smoke constituents. Self-reported exposure to ETS as well as the use of biomarker like nicotine or cotinine are certainly valid means to help epidemiologists register the extent of such exposure. However, its significance in terms of increased incidence of lung cancer in non smokers cannot simply be derived from syllogisms. For a molecular toxicologist, such a conclusion can only rely on a quantitative biomonitoring of exposure to agents proven to play a causative role in lung carcinogenesis.

Definitions

Environmental tobacco smoke or ETS:
A mixture of diluted and aged gases and solid suspended particles resulting from a combination of sidestream smoke (SS) (80-90%) and exahled mainstream smoke (EMS) (10-20%).

Mainstream smoke or MS:
The cigarette smoke drawn through the tobacco into smoker's mouth.

Exhaled mainstream smoke or EMS:
The fraction of MS not retained by the smoker and exhaled in the air (EMS is not identifical to MS because it has been substantially depleted in vapor phase constituents and because the particulate matter is likely to have increased its water content).

Sidestream smoke or SS:
The smoke emitted by burning tobacco between puffs and/or the aerosol emitted in the surrounding air from a smoldering tobacco product between puff drawing and/or all of the tobacco smoke issued apart from the MS which is delivered to the smoker.

Respirable suspended particles or RSP
The solid phase of the aerosol.

Table 1 Definitions (1, 2, 3).

Indeed, since the exposure level to ETS is likely to be low compared to active smoking (3,6), since many confounding factors (like radon exposure, misclassification of light smokers, former smoking habits, and dietary factors) are likely to exist, one has to recognize that the classic epidemiological methods alone may not be sufficiently sensitive for scientifically establishing that ETS exposure plays a significant role in the incidence of lung cancer in ETS-exposed non smokers (3). Such a conclusion needs to be supported by dosimetry which not only confirms personal records of ETS exposure in quantitative measures of a reliable parameter, but also demonstrates that such an exposure has indeed led to a significant intake of carcinogenic components. Various biomarkers of exposure to cigarette smoke [see Table 2 (3, 7-10)] have already been proposed with the aim of developing a quantitative approach to the epidemiology of diseases in non smokers, particularly lung cancer. These include measures of plasma, salivary and/or urinary concentrations of either (a) a major, specific tobacco smoke molecule and/or its main metabolites or (b) the end-products of the metabolic activation of carcinogenic components in tobacco smoke.

The aims of the present paper are :

1) to review the data on the quantitative biomonitoring of exposure to ETS based on nicotine and/or cotinine measurements in physiological fluids.

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2) to discuss the relevance of these biomarkers in assessing any increase in lung cancer incidence associated with exposure to ETS;
3) to propose new approaches likely to be more scientifically relevant to evaluate exposure to ETS for risk

BIOMONITORING ETS EXPOSURE: A REVIEW OF THE DATA

The optimal assessment of exposure to ETS should derive from measurements of the relevant biomarkers made on easily accessible physiological fluids by using a simple, readily available analytical method. Biomarkers are "an measure of dose or uptake and hence an indicator that an exposure has taken place" (5).

An ideal biomarker of exposure to ETS (5, 10) must:

a) be chemically specific to ETS;
b) have a long half-life in the body;
c) be present in sufficient quantity in tobacco smoke so that it can be measured even at low levels of ETS exposure;
d) be characterized by similar emission rates for a variety of tobacco products;
e) be in a fairly constant ratio to different combustion products of tobacco smoke constituents accross different brands of cigarettes and for a range of environmental conditions encountered;
f) be either the agent which is associated with the suspected effect(s) or strongly associated with the agent of interest.

Of the biomarkers [Table II (3, 7-10)] which have, up to now, been developed to a significant stage to monitor tobacco smoke exposure by active smokers, only nicotine and its metabolite cotinine have been used repeatedly to monitor exposure to ETS. Indeed, they have been proposed as the most specific and the most sensitive markers presently available (11). But, as underlined in the US-EPA document (5): "although these biomarkers (may) demonstrate that an exposure has taken place, they may not be directly related to potential for development of the adverse effect under study."

Data (Table III and IV, [7, 12-23]) show that non-smokers [illegible] ETS [illegible] [illegible] [illegible]

nine/24h are meaningful. The general conclusions of these studies are that:

a) the experimental data are not always comparable [illegible] different studies, in particular with regard to uri-

[illegible] longer half-life, cotinine is likely to be a more suitable marker than nicotine.

[illegible] urinary concentrations of cotinine correlate with serum concentrations.

d) passive smokers have, in their physiological fluids, concentrations of cotinine equivalent to few ng/ml or ng/mg creatinine as compared to hundreds or thousands of ng/ml or ng/mg creatinine in active smokers.

e) such parameters might be valid for estimating acute exposure to relatively high levels of ETS.

f) at low levels of exposure to ETS, non-smokers have concentrations of nicotine and/or cotinine in their biological fluids, which are not very different from those measured in non-smokers not exposed to any identified ETS [Table III and IV (7, 12-27)]. As early as 1984, Jarvis *et al.* (7) reported that "the majority of non-smokers in UK may have measurable amounts of tobacco-specific chemicals in body fluids". Proctor *et al.* (13) have also expressed their "doubts about the validity of salivary cotinine at low levels". Moreover, in a large nationwide survey conducted in the US under the auspices of the CDC's National Center for Environmental Health and the National Center for Health Statistics (28), 100% of the 800 persons so far analysed were reported to have measurable levels (0.03 to 650 ng/ml) of cotinine in their serum. There is no reason to believe that all these people either smoke or are exposed to ETS. If confirmed, such an observation would have important practical consequences. Indeed, when correlating urinary cotinine as a biomarker of ETS exposure with increased risk of lung cancer, one would have to refer to increased urinary cotinine concentrations (meaning the difference between ETS exposed and non-exposed individuals) but not to absolute values.

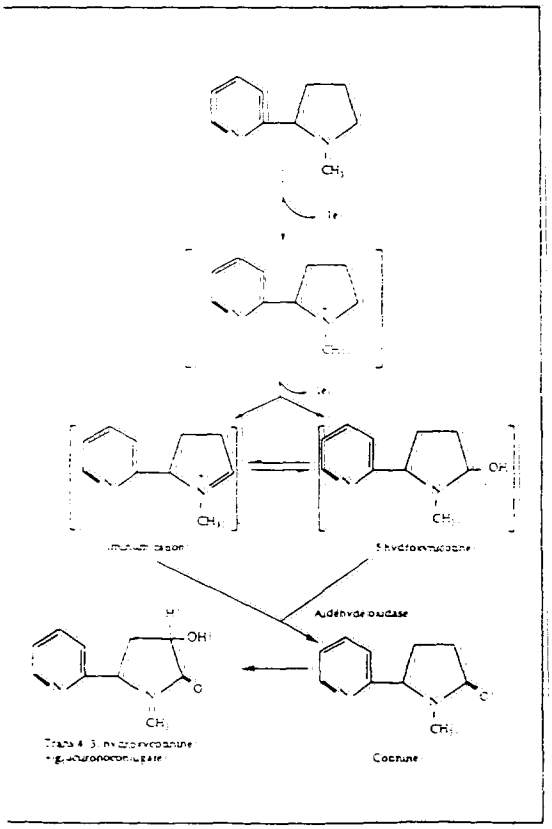

Fig. Major metabolic pathways of primary C-oxidations of nicotine in humans

ARE NICOTINE AND/OR COTININE RELEVANT BIOMARKERS FOR CORRELATING ETS EXPOSURE WITH INCREASED INCIDENCE OF LUNG CANCER ?

As indicated above, a relevant biomarker must be unique to the source of exposure. But nicotine, and consequently its metabolite cotinine, are not unique to tobacco smoke. It is present in edible plants of the family of *Solanaceae* (like potatoes, tomatos...) as well as in a number of teas, especially instant tea. Davis *et al.* (29) have calculated a range of potential values for urinary cotinine concentrations (0.6-6.2ng/ml) based upon estimated average and maximal consumption of foods and beverages; nicotine is also consumed as nicotine gums or nicotine dermal patches as well as in chewing or wet snuffing of tobacco. Finally, nicotine is still used as an insecticide in the form of decoctions of tobacco leaf and it is known that nicotine persits in soil. Besides ETS, miscellaneous sources of exposure to nicotine thus exist. They may contribute significantly to the build-up of its metabolite(s) in the plasma, saliva and urine of non-smokers. Because of its short half-life in humans (30-33), nicotine is not a valuable marker. This is the reason why cotinine is classically used to biomonitor exposure to tobacco smoke, including passive smoking. However, large interindividual variations exist in the biodisposition of cotinine, as shown by the sometimes large variabilities in reported urinary excretion (14, 15, 17-19). Moreover this metabolite would be a relevant biomarker for ETS exposure only if it is one of the major end-metabolites of the parent compound. However this is not the case. Indeed, nicotine is extensively metabolized (Fig 1) via a human cytochrome P450-dependent mixed function oxidase to form the iminium ion which is then oxidised, by a soluble aldehyde oxidase (34, 35), to cotinine (36, 37). This metabolite does not readily accumulate because it is further hydroxylated to 3'-hydroxycotinine (either free or glucurono-conjugated) the major excreted human metabolite of nicotine (38-43). Thus, from a strictly pharmacokinetic point of view, the relevance of cotinine measures for biomonitoring tobacco smoke exposure, particularly at low levels, is questionable. At the very least, studies need to be performed to compare both cotinine and 3'-hydroxycotinine as potential markers for exposure to nicotine.

Another question which also needs to be addressed is the ratio of nicotine (and thus indirectly cotinine or 3'-hydroxycotinine) to other tobacco smoke constituents (for example polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines...). Is this ratio constant enough for measurement to be extrapolated to the other? To meet such a

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requirement, it has to be demonstrated that the ETS to which non-smokers are exposed has the same composition as MS, the reference product for defining potential risk of lung cancer. However, ETS is composed of SS (75-80%) and EMS (20-25%) which are both physically, as well as chemically, different from MS (2, 3, 8, 44). The differences between MS and SS, which are relevant to our discussion, are attributable to differences: [1] in the temperature of combustion of the tobacco (900°C and 600°C respectively) [2] in the pH (6.0-6.5 and 6.5-7.5 respectively) [3] in the degree and the rate of dilution with air, [4] in the size of RSP (0.1-1.0 and 0.01-1.0 microns respectively), and [5] the relative composition of the gas as compared to the particle phase (particularly nicotine, which is predominantly in the particle phase of MS but in the vapor phase of SS). Knowledge of the composition of EMS is very limited and comparative analysis have not been reported. Thus, it is likely that ETS may contain most of the chemicals so far identified in MS. But, as underlined in the US-EPA document (5), "few emission data have been collected under conditions more typical of actual smoking conditions....[and] it is not known how the MS and SS air contaminant emission data for specific compounds generated by standardized testing protocols compare to data gathered under conditions more representative of actual smoking".

The last point concerns the bioavailability of nicotine, which, according to various reports, differs significantly between individuals and in non smokers as compared to active smokers (23, 24, 30). Indeed, high doses of MS induce the enzymes metabolizing not only nicotine but also a wide variety of xenobiotics. This effect is unlikely to occur in non smokers exposed to low doses of ETS.

As a consequence of these differences between MS and ETS, estimates of ETS exposure based on measures of nicotine and/or its metabolite(s) in biological fluids of non-smokers (except perhaps in short-term acute and quite unusual exposure to high dose of ETS) is likely to be misleading, at least in terms of increased lung cancer incidence. Furthermore, because of the differences between ETS and MS as well as because of interindividual variations in biodisposition of nicotine, it is difficult to anticipate whether the values will be over or underestimated (17, 45). A recent paper (46) reports data in guinea pigs exposed to MS or SS which demonstrate that urinary cotinine (ng/mg creatinine) does not correlate with the total amount of inhaled RSP (mg/kg bw/day). In animals exposed to MS or SS from 6 (54 puffs) or 8 (70 puffs) cigarettes, total inhaled RSP were 23 ± 0.7 and 28.3 ± 1.4 mg/kg bw/day respectively after MS exposure, but only 1.5 ± 0.4 and 1.8 ± 0.4 mg/kg bw/day after SS exposure. In the same animals, urinary cotinine (ng/mg creatinine) reached 8.1 ± 2.3 and 10.3 ± 1.8 respectively after inhalation of MS and 3.7 ± 0.15 and 10.6 ± 1.5 respectively after exposure to SS. Based on these data, the calculated ratios between the amount of absorbed RSP and the quantity of urinary cotinine, expressed as mg RSP /kg bw/day per ng cotinine are 2.7 and 2.9 after inhalation of MS but only 0.17 and 0.4 after exposure to SS. Since ETS is mainly composed of SS, such data, if indeed applicable to human exposure, would indicate that an equal amount of urinary cotinine, in MS versus SS (ETS)-exposed individuals, represents quite a different exposure to RSP. Al though they may excrete the same amount of urinary cotinine, SS (ETS)-exposed people might have been exposed to 10 times less RSP than MS-exposed smokers, a conclusion which is consistent with the differences in distribution of nicotine between vapor and particulate phases of MS and ETS.

NEW DIRECTIONS TOWARDS A MORE RELEVANT BIOMONITORING OF ETS EXPOSURE SO AS TO CORRELATE WITH INCIDENCE OF LUNG CANCER IN NON SMOKERS.

For ETS to be considered as a risk factor for lung cancer in non smokers, calculations should be based on defined exposure to relevant chemicals. Neither nicotine nor its metabolites are likely to be precise markers of exposure to such chemicals which are mainly bound to RSP; whereas nicotine is in the vapor phase of ETS. Monitoring of ETS exposure should rely on measurements of bioproducts in physiological fluids which are directly and quantitatively derived from constituents like polycyclic aromatic hydrocarbons, aromatic amines or nitrosamines.... which are mainly in RSP (17, 47). Molecular epidemiology, as it has developed during the last decade, offers a promising, but still to be validated, tool to meet such a challenge by measuring proteins and/or DNA adducts in serum or urine samples (48, 49).

Specific and very sensitive analytical methods (50, 51) as well as molecular biology techniques able to identify and quantify modified nucleotides in DNA or modified proteins are presently available, and should be applied to correlate objectively lung cancer with exposure to specific chemicals in non smokers. They are indeed unique in providing the specificity which is required to precisely quantify precisely the low levels of exposure occuring in involuntary absorption of ETS. Such an approach would meet the requirements discussed by Monro (52) under the title "Contemporary Issues in Toxicology: What is an appropriate measure of exposure when testing drugs for carcinogenicity in rodents?" By reference to the concept of biologically effective dose introduced by Perrera (53), Monro (52) underlines that "the toxicity of the drug was not reflected by its plasma concentration; instead it depended on the amount converted to a reactive metabolite which then went on to bind with a critical macromolecule" and that "when chemical carcinogenesis is mediated via a reactive metabolite binding covalently to a critical macromolecule ..... the first determinant of the biologically effective dose is that proportion of the administered dose that is converted to the key reactive metabolite. The consequence ... may be also influenced by the rate at which the reactive metabolite becomes available, which in turn may depend on the rate of drug administration...a brief high pulse of reactive metabolite [as it occurs in inhalation of MS] could have different consequences from a prolonged lower delivery rate [as it occurs in ETS exposure] ...". This discussion is relevant to our subject. Indeed, only the evaluation of the biologically effective dose is likely to allow a correct biomonitoring of exposure to be used for conclusively correlating exposure to ETS with any increased incidence of lung cancer. A similar proposal was made by

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Lucier (ref 49) in a symposium held at the 29th annual meeting of the Society of Toxicology. This topic has recently been reviewed extensively in the excellent article of Grosman and Kensler (54) entitled "Molecular bio- [illegible] chemical carcinogen exposures."

One candidate chemical for such an approach is the aromatic amine 4-aminobiphenyl (4-ABP). Because its concentration is higher (ca. 30 times) in SS, it might be a more reliable biomarker for exposure to ETS than nicotine. Metabolic activation and covalent binding to macromolecules, in particular hemoglobin (Hb), yields an adduct. This might serve as a surrogate marker for DNA adducts to evaluate a biologically effective dose (55). Available data, although still preliminary, show that the methods are indeed adequate to assay the low levels of adducts found in the biological fluids of non smokers (a few pg/g Hb) and that a relationship might exist between exposure to ETS and the levels of 4-ABP-Hb adducts in non smokers (9, 55-58). Such a new experimental approach will require extensive research before being validated to assess real exposure to ETS and to establish a link between such an exposure and increased risk of lung cancer. Among other questions which need to be answered are: [1] the specificity of ETS as a source of 4-ABP; [2] the pharmacokinetics of 4-ABP-Hb adduct formation in human blood and relating its level to the time, duration, frequency of exposure to well defined ETS; [3] the quantitative, if any, relationship between a specific "dose" of ETS and the blood level of the adduct; and [4] the correlation, if any, between the 4-ABP-Hb adduct and other adducts likely to be formed because of exposure to other agents. Indeed, 4-ABP is not recognized as a lung but rather as a bladder carcinogen, and there is no convincing epidemiological evidence to suggest that the risk of bladder cancer is increased in non smokers. Since polycyclic aromatic hydrocarbons and in particular benzo(a)pyrene (59), as well as nitrosamines (50), also form adducts, it seems reasonable to at least explore these possibilities.

CONCLUSIONS

ETS is a complex mixture [illegible] of gases and RSP. There is no doubt that people living in the proximity of an active smoker are exposed to and absorb constituents of ETS. However, it is both a highly diluted and an aged mixture, the composition of which is qualitatively and quantitatively different from MS. When epidemiologists work to correlate low levels of ETS exposure with an increased risk of lung cancer they should be advised not to rely only on questionnaire results because of the many biases. Quantitative molecular epidemiology will help to resolve the question of the actual risk of such exposure. However, the relevant marker remains to be chosen. Neither nicotine nor its metabolites fulfil the criteria. Quantitative measurements of molecular adducts to macromolecules might be promising tools, but many basic questions still need to be answered before they can be applied routinely. These basic questions concern not only the analytical aspects, but also the mechanisms of any toxic potential, including the cause of large interindividual variations in metabolic capacity for activation and inactivation of carcinogens as well as in repair mechanisms (59) that might explain any increased incidence of lung cancer. Indeed, quantitative molecular epidemiology will contribute to a better correlation between ETS exposure and increased risk of lung cancer in non smokers only if it continues to benefit from progresses in basic research in toxicology. Indeed, as we have discussed repeatedly, to improve the science in toxicology is the necessary key to real progress in risk assessment (59). To correlate the concentration of a particular macromolecular adduct with increased risk of lung cancer in non smokers exposed to ETS will benefit from any data which support the hypothesis of a causal relationship between the *in vivo* concentration of an adduct and the pathogenic process leading to the disease. ■

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Corrélation entre le tabagisme passif et l'incidence accrue de cancers pulmonaires: la cotinine est-elle un marqueur valide ?

RESUME

La fumée du tabac présente dans l'environnement est un mélange complexe de la fumée exhalée par le fumeur et la fumée qui s'échappe du tabac en combustion. Cette fumée est composée de substances volatiles et de particules solides en suspension qui forment un aérosol respirable. Elle est tout à la fois très diluée et vieillie par rapport à une fumée inhalée dont la composition est qualitativement et quantitativement différente. En utilisant deux syllogismes, l'hypothèse a été émise que l'exposition à de faibles doses de fumée de tabac présente dans l'environement augmente le risque de cancer du poumon chez les non-fumeurs. Il est évident que les non-fumeurs qui vivent en présence d'un fumeur sont exposés à certains constituants de la fumée du tabac. Toutefois, pour pouvoir conclure à la signification d'une telle exposition, en terme d'incidence accrue de cancer du poumon chez les non-fumeurs, il importe de disposer des résultats quantitatifs qui démontrent une exposition à des agents connus pour jouer un rôle causal dans la cancérogenèse pulmonaire. Ni la nicotine, ni ses métabolites ne sont des marqueurs précis de l'exposition à de tels agents cancérigènes. L'épidémiologie moléculaire permet d'envisager une approche de cette question en mesurant des adduits aux protéines ou à l'ADN dans le sérum ou les urines. Toutefois, une telle approche doit encore être validée.

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